Remarks

Rejections under 35 U.S.C. § 101

Claims 92, 93, 95, 97, 103-105, and 107 stand rejected under 35 U.S.C. § 101 as being drawn to non-statutory subject matter on the ground that they read on a product of nature, e.g., antibodies present in the serum of an infected individual. The Examiner states that like the claimed invention serum contains a combination of antibodies. Applicants respectfully traverse the rejection on the ground that the claims all recite a combination of *isolated* antibodies and are thus distinct from serum. Withdrawal of the rejection is respectfully requested.

Objections

Claims 26-27 are objected to for depending from a rejected base claim. As indicated below, the base claim is allowable, thereby rendering claims 26-27 allowable also.

Rejections under 35 U.S.C. § 102

Claims 92, 93, 95, 97, 103-105, and 107 stand rejected under 35 U.S.C. § 102 as being anticipated by Mehta, et al., U.S. Pat. No. 5,308,750, hereinafter "Mehta". The Examiner states that these claims read on a product of nature, namely human serum from an individual infected with HCV, and that since Mehta discloses isolating human serum from an individual infected with HCV, Mehta anticipates the subject matter of the instant claims. As pointed out above in the remarks addressing the rejection under 35 U.S.C. § 101, the instant claims do not read on human serum because they recite a combination of *isolated* antibodies. Therefore the claims are not anticipated by Mehta. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1, 8, 9, 12, 14-22, 25, 28, and 106 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Mehta. The Examiner first states that Mehta discloses an antibody selected from CBH-2, -4G, -5, -7, -8C, and -11 or an antibody that recognizes the same epitope as one of these antibodies since Mehta discloses an antibody that recognizes an epitope between positions 607-627. The Examiner then argues that it would have been obvious to use the epitope defined by positions 607-627 to manufacture and isolate antibody and thereby arrive at the

claimed invention. Applicants respectfully traverse the rejection for each of the following reasons.

First, Mehta does not provide motivation to use the epitope defined by position 607-627 to manufacture and isolate antibody. Mehta indicates that four amino acid sequences were identified as immunogenic, namely 607-627, 643-663, 666-683, and 671-691 (col. 11, lines 25-28). However, Mehta selects amino acids 643-683, i.e., "the combination of the two most immunogenic sequences" as the immunogen for monoclonal antibody production (col. 11, lines 33-34). Thus the amino acid sequence 607-627 displayed lower immunogenicity than two of the other three sequences. One of ordinary skill in the art would therefore not have been motivated to select this sequence as an immunogen, since the likelihood of successfully raising useful antibodies would have been lower than the likelihood if alternate sequences taught by Mehta were used. Furthermore, Mehta showed successful production of antibodies using 643-683 as an immunogen. The Examiner has not provided any reason why there would have been motivation to try to make alternative antibodies using an immunogen that Mehta evidently considers to be inferior.

Second, contrary to the Examiner's assertion, one of ordinary skill in the art would not have had a reasonable expectation of success in manufacturing an isolated antibody against positions 607-627 by using the epitope defined by position 607-627. Mehta teaches that sera from individuals seropositive to antibodies to HCV proteins reacted with this amino acid sequence (col. 11, lines 4-30). However, Mehta does not provide any evidence that the epitope to which the sera reacted consisted solely of amino acids between positions 607-627 or that immunization with a peptide consisting solely of this region would result in successful production of antibodies.

Third, the Examiner has provided no evidence that the antibody disclosed by Mehta as recognizing an epitope between positions 607-627 is "selected from CBH-2, -4G, -5, -7, -8C, and -11, or an antibody that recognizes the same epitope as one of these antibodies". The claims are not drawn to every antibody that binds to any epitope within the regions of 411-644 or 470-644. The claims are instead drawn to antibodies that bind to specific conformational epitopes that lie

within these regions. The claims do not recite that the antibodies bind to an epitope between positions 607-627, and absent evidence to the contrary there is no reason to believe that they do. The fact that positions 607-627 lie within the broader regions that contain the conformational epitopes to which the claimed antibodies bind does not establish that the claimed antibodies would bind to an epitope between 607-627. Thus even if there had been motivation to try to produce antibodies that bind to an epitope between 607-627 by using amino acids 607-627 as an immunogen, and even if there had been a reasonable expectation of success, there is no evidence that the resulting antibodies would recognize the same epitopes as the claimed antibodies.

Fourth, as shown by the data presented in the accompanying Declaration under 35 U.S.C. 132 of Dr. Steven K. Foung, an antibody that was manufactured using amino acids 607-627 as an immunogen would not, in fact, bind to the same epitope as do the claimed antibodies.

The Declaration describes experiments that were performed to determine the regions of HCV E2 that contain the binding sites for the antibodies. A series of deletion constructs containing coding sequences for amino acids 384-661 of the HCV E2 polypeptide, or fragments thereof that contain either N- or C- terminal deletions, was expressed using the pDisplay vector, which results in expression of a polypeptide of interest on the surface of a cell into which the vector is transfected. The ability of the claimed antibodies to react with polypeptides containing amino acids 384-661 of HCV E2 or various fragments thereof was assessed by flow cytometry. It is noted that the experiments described in the Declaration are similar to those described in Example 9 of the specification at p. 77, line 18 – p. 79, line 21 (Methods) and p. 86, line 8 – p. 87, line 10 (Results), except that they utilized a larger collection of deletion constructs, allowing a more precise determination of the regions of HCV E2 that contains the binding site for the antibodies.

As described in the Declaration, results obtained using these deletion constructs showed that the epitopes to which antibodies CBH-2, CBH-4G, CBH-5, CBH-7, CBH-8C, and CBH-11 bind are not located between positions 607-627 because these antibodies do not bind to fragments of E2 that encompass amino acids 607-627. For example, these antibodies do not bind to a polypeptide that contains amino acids 600-661 of HCV E2, which encompasses amino acids 607-627. Instead, these antibodies also require the presence of at least some amino acids located between positions 384-600 in order to show reactivity.

Furthermore, the epitope to which CBH-4B and CBH-4D bind encompasses at least some amino acids between amino acids 384-600, since the presence of those amino acids in addition to amino acids 600-661 resulted in greatly increased binding. Therefore, the epitope recognized by CBH-4B and CBH-4D cannot lie entirely within HCV E2 amino acids 607-627. Thus an attempt to manufacture antibodies using only HCV E2 amino acids 607-627 as an immunogen would not result in the claimed antibodies.

In summary, for each of these four reasons, Mehta does not render the instant claims obvious. Withdrawal of the rejection is respectfully requested.

In conclusion, in view of the remarks presented herein and the accompanying Declaration under 35 U.S.C. § 132, Applicants respectfully submit that the claimed invention meets the requirements of 35 U.S.C. § 132 and is not obvious in view of Mehta. Applicants therefore respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial).

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Respectfully submitted,

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